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IN RE APPLICATION OF: Francesco PARENTI, et al.

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FOR: NEW INJECTABLE FORMULATIONS CONTAINING RAMOPLANIN

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO.	DAY/MONTH/YEAR
EUROPEAN PATENT OFFICE	98114368.8	30 July 1998

A certified copy of the corresponding Convention application(s) was submitted to the International Bureau in PCT Application No. **PCT/EP99/05137.** Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

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Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

98114368.8

PRIORITY DOCUMENT
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Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

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Sheet 2 of the certificate
Page 2 de l'attestation

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NEW INJECTABLE FORMULATIONS

The present invention relates to a new injectable formulation of ramoplanin or a compound of the ramoplanin family. More particularly, the injectable formulations of the invention are particularly suitable for intravenous (i.v.) administration.

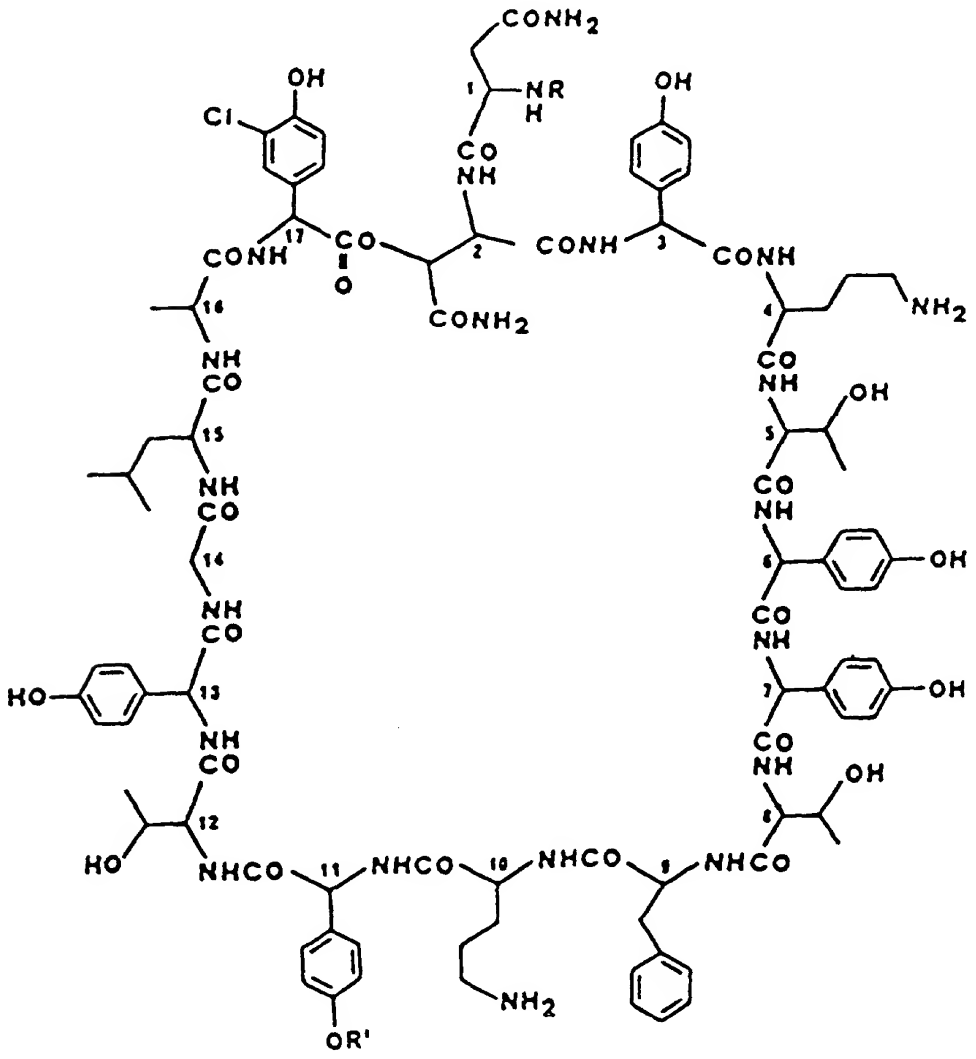
Ramoplanin (INN) is a known member of the cyclic peptide antibiotics more precisely known as lipodepsipeptides which has been described in US 4,303,646 and 4,328,316. Originally it has been named antibiotic A 16686. It is a complex substance whose separate factors A_1, A_2 and A_3 have been described in US 4,427,656.

Ramoplanin factors A'_1, A'_2 and A'_3 have been described in EP-B-318680, the aglycones of any of the above factors have been described in US 5,491,128 while the tetra hydrogenated derivatives of any of the above factors have been described in US 5,108,988. All the above mentioned patents are incorporated herein by reference.

The structure of ramoplanin and its factors and derivatives have been described in several articles and publications, see R. Ciabatti et al., J. Antib. 1989, 254-267, J. K. Kettenring et al., J. Antiob. 1989, 268-275, R. Ciabatti and B. Cavalleri, Bioactive Metabolites from Microorganisms, Elsevier Science Publisher, 1989, 205-219 and M. Kurz and W. Guba, Biochemistry 1996, 35, 12570-12575.

N.J. Skelton et al. in J. Am. Chem. Soc. 1991, 113, 7522-7530 describe another member of this family, which they call Ramoplanose.

These compounds can be represented by the following formula (Formula I):



FORMULA I

wherein:

R represents $-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3$,
$-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,
$-CO-CH=CH-CH=CH-CH_2-CH_2-CH(CH_3)_2$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)_2$ or
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)_2$

R' represents alpha-D-mannopyranosyl or 2-O-alpha-D-mannopyranosyl, or

R' represents 2,3-O-di[alpha-D-mannopyranosyl]-D-mannopyranosyl when R represents $-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,

a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof in any proportion.

The configuration of the double bonds of the unsaturated moieties reported above in the definition of R have been found to be 2(E) or *cis* and 4(Z) or *trans* in the literature reported above.

The following table specifies the meanings for R and R' of the single factors or derivatives with reference to the above formula:

Factor	R	R'
A_1	-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3	2-O-alpha-D-manno-pyranosyl-alpha-D-mannopyranosyl
A_2	-CO-CH=CH-CH=CH-CH_2-$CH(CH_3)_2$	2-O-alpha-D-manno-pyranosyl-alpha-D-mannopyranosyl
A_3	-CO-CH=CH-CH=CH-CH_2-CH_2-$CH(CH_3)_2$	2-O-alpha-D-manno-pyranosyl-alpha-D-mannopyranosyl
A'_1	-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3	Alpha-D-mannopyranosyl
A'_2	-CO-CH=CH-CH=CH-CH_2-$CH(CH_3)_2$	Alpha-D-mannopyranosyl
A'_3	-CO-CH=CH-CH=CH-CH_2-CH_2-$CH(CH_3)_2$	Alpha-D-mannopyranosyl

The aglycones correspond to the compounds reported above wherein R' represents hydrogen while the tetrahydrogenate derivatives correspond to the compounds reported above wherein the mojety R is fully hydrogenated.

Ramoplanose is reported to correspond to "factor A_2" wherein R' represents 2,3-O-di[alpha-D-mannopyranosyl]-D-mannopyranosyl.

In the following description and claims, the term "ramoplanin" refer to a ramoplanin complex wherein factor A_2 is the major component, with a small amounts of factors A'_2, A_1, A'_1, A_3, A'_3 and other related substances accounting for the remainder of this active ingredient.

Particularly preferred is "ramoplanin" wherein factor A_2 represents at least 75% of the active ingredient.

"A member of the ramoplanin family" refers to any of the compounds reported above that are represented by Formula I, any salt or any mixture thereof in any proportion.

Ramoplanin as well as any members of the ramoplanin family are unsuitable for i.v. administration because of drawbacks such as swelling and progressive necrotization at the site of injection, and haemolysis as revealed by urine discoloration.

The formulations of the invention contain ramoplanin or a member of the ramoplanin family in admixture with a fat emulsion product for intravenous administration.

In the current description and claims "a fat emulsion product for intravenous injection" is any of those fat emulsion products suitable for intravenous administration via a peripheral vein or by a central venous infusion that are currently used for example to prevent fatty acid deficiencies when prolonged parenteral nutrition is required. Examples of these substances are for instance reported in US Pharmacopeia, Martindale, The Extra Pharmacopeia (31st edition, 1996, page 1377) or VIDAL 1996, page 814.

They are largely based on vegetable oils (10-20% vol/vol) stabilized by phosphatides (1-2% w/vol).

Typically, a fat emulsion suitable for preparing a formulation of the invention comprises vegetable oils

such as soybean or safflower oil, phospholipids such as egg yolk phospholipids, glycerin, fatty acids such as linoleic, oleic, palmitic, linolenic or stearic acid and any mixtures thereof.

These fat emulsion products are dispersed in water for injection and the fat product is generally present in the emulsion in a percentage (weight/weight) of 5 to 25%.

Preferred for the formulations of the invention are those fat emulsions wherein the fat product is between 7 and 15%, and more preferably between 8 and 10%, with 10% being currently the most preferred concentration.

The fat emulsion product is generally a mixture of the above indicated components in varying proportion.

Generally, the osmolarity of the emulsions is between 250 and 300 mOsm/L, while the approximate pH is generally between 7.8 and 8.5.

As known in the art, particle size needs to be controlled for a proper i.v. administration, and this is accomplished through the conventional preparation and final formulation procedures.

Examples of fat emulsion products that can be conveniently used according to the present invention are those which contain a mixture of soybean oil, safflower oil, egg yolk phospholipids, glycerin and fatty acids comprising mainly linoleic acid, oleic acid, palmitic acid, linolenic acid and stearic acid.

These fat emulsion products are then dispersed in water for injection to a final concentration that is preferably between 10% and 20%.

Currently preferred are those fat emulsion products that are currently available under the trade names Intralipid (Kabi Vitrum/Pharmacia) and Lyposyn II and Lyposyn III (Abbott) whose composition and physico-chemical properties are reported below:

Table I. Composition and characteristics of Various Intravenous Fat Emulsions

Components or Characteristics	Intralipid (Kabi-Vitrum/Pharmacia)			Liposyn II (Abbott)			Liposyn III (Abbott)		
Soibean oil	10%		20%	5%		10%	10%		20%
Safflower oil	--		--	5%		10%	--		--
Egg yolk phospholipids	1.2%		1.2%	1.2%		1.2%	1.2%		1.2%
Glycerin	2.25%		2.25%	2.5%		2.5%	2.5%		2.5%
Water for injection	QS		QS	QS		QS	QS		QS
Fatty acids:									
Linoleic acid		50%			65.8%			54.5%	
Oleic acid		26%			17.7%			22.4%	
Palmitic acid		10%			8.8%			10.5%	
Linolenic acid		9%			4.2%			8.3%	
Stearic acid		3.5%			3.4%			4.2%	
Osmolarity (mOsm/L)	260		268	276		258	284		292
Approximate pH	8		8	8		8.3	8.3		8.3
Fat particle size (μm)	0.5		0.5	0.4		0.4	0.4		0.4
Caloric value (cal/ml)	1.1		2.0	1.1		2.0	1.1		2.0
Size (ml)	5, 100		50, 100	25, 50		25, 50	100,200		200,500
	250,500		250,500	100,200		200,500	500		
				500					

Ramoplanin or an antibiotic of the ramoplanin family as defined above is generally present in the compositions of the invention in an amount of 5 to 20 mg/ml, with about 10 mg/ml being currently preferred.

Typically, the composition of the invention is a composition wherein the fat emulsion product is between 4 and 20%, 6-18% being preferred and with 8-10% being currently most preferred.

Experiments with representative examples of the compositions of the invention have shown a good tolerability at the site of injection, in particular in comparison with the effects of conventional i.v. preparations of the same active principle.

The results of tolerability studies of representative examples of formulations of the invention in rats at a concentration of ramoplanin of 10 mg/ml (dose 20 mg/kg, administration volume 2 ml/kg), in comparison with a conventional i.v. formulation of the same active principle, are summarized in the following table.

More particularly, Ramoplanin in a conventional acqueous vehicle (0.9% saline) or in the formulations of the invention wherein the fat emulsion product is between 2 and 8% is administered to rats (3-5 animal/group) at a dose of 20 mg/kg (drug concentration 10 mg/ml). The administered volume is 2 ml/kg, according to the animal weight on the day of administration, and the injection speed is 0.1 ml/sec. The intravenous administration is into the caudal vein. Treatments are planned for three days at 24 hours intervals. Control rats receive either 0,9% saline or an equivalent volume of a 10% aqueous solution of the

fat emulsion product. Behavior and physical appearance are observed frequently the day of dosing. Urine appearance is also recorded within 3 h after each daily treatment. Rats are sacrified 24 h after the last treatment. The results of these experiments are summarized in Table II.

Table II. Urine appearance, gross pathology at the injection site and clinical observations of rats treated with ramoplanin formulated with Intralipid or in a conventional acqueous vehicle (0.9% saline)

Groups	No. Animals	Saline	Intralipid (a)	Ramoplanin	Urine Appearance (b)	Gross Pathology at the injection site (c)
A	3	0.9%	--	--	Normal	Normal
B	4	0.9%	--	10 mg/mL (d)	Red-brown	Dark, discolored tails
C	3	--	10%		Normal	Normal
D	5	--	8%	10 mg/mL	Normal	Normal
E	5	--	4%	10 mg/mL	Normal	Normal
F	5	--	2%	10 mg/mL	Red-brown	Dark, discolored tails

(a) In water for injection, q.s. 100%

(b) Visual examination performed within 2-3 h after each scheduled treatment

(c) Examinations performed at the end of the three scheduled treatments

(d) Corresponding to a dose of 20 mg/kg

Treatments with ramoplanin in conventional aqueous vehicle or in formulation with 2% of fat emulsion product caused darkness or discoloration at the injection site (tail). In contrast, treatment with the formulations of the invention wherein the fat emulsion product was 4% or higher was well tolerated. Tails did not show any sign of necrotic inflammation.

After the immediate postdose period of each treatment (3 h) with the formulations of the invention wherein the fat emulsion product is 4% or higher, the urine appeared light straw to dark yellow in colour. In contrast, rats given a 2% formulation of the fat emulsion product or ramoplanin in conventional aqueous vehicle developed red to red-brown urine, within the same postdose period.

The effectiveness of representative examples of the compositions of the invention in experimental animal models can be demonstrated in several acute septicemia experiments in immunocompetent or neutropenic mice and in experiments of endocarditis and pneumococcal lobar pneumonia in rats.

Experimental septicemia is induced by inoculating intraperitoneally (5-6 animal/dose/treatment group) a bacterial suspension of either a clinical isolate of a methicillin resistant staphylococcus (*Staph. aureus* L613) or streptococcus strain (*Strep. pneumonia* L 44) in immunocompetent mice or a clinically isolated glycopeptide resistant enterococcus strain (*Ent. faecium* L569) in neutropenic mice. Immunocompetent mice are male and female CD_1 mice (Charles River Labs., Calco, Italy) weighting 18-22 g while neutropenic mice

are 6-8 weeks old female NMRI mice (Iffa Credo, France).

Untreated animals die within 24-72 h after infection. Antibiotic treatment begins within 10 min after injection. Ramoplanin is administered intravenously in conventional aqueous vehicle or in the formulation of the invention in 10% fat emulsion product. Gentamicin, vancomycin, teicoplanin and rifampicin can be included as comparator drugs. The 50% effective dose (ED_{50}) and 95% confidence limits are calculated by the Spearman-Karber method from the percentage of animal surviving at day 10.

The animals are treated twice, first 10 min from infection and then 24 h later.

When the gentamicin or vancomycin are employed as comparators, they are administered subcutaneously and the second shot is given 5 h after infection. Rifampicin follows the general scheme, but it is administered subcutaneously, while teicoplanin is administered subcutaneously in single dose 10 min after infection.

Results of experiments conducted as described above are reported in the following table:

Table III. ED_{50} of ramoplanin in experimental septicemia in mice.

Strain (animal)	Formulation	ED_{50} mg/kg/dose (95% confidence limits)
VanA *Ent.faecium* L 569 (neutropenic mice)[a]	Ramoplanin in 0.9% saline	5.1 (d)
	Ramoplanin in 10% intralipid	1.7 (1.4-2.0)
Staph. aureus L 603 (immunocompetent mice)[b]	Ramoplanin in 0.9% saline	4.3 (3.1-6.0)
	Ramoplanin in 10% intralipid	5.1 (3.9-6.5)
Strep. pneumonia L 44 (immunocompetent mice)[c]	Ramoplanin in 0.9% saline	0.06 (d)
	Ramoplanin in 10% intralipid	0.06 (d)

[a] ED_{50} of comparators were as follows: gentamicin 50.6 (37.3-68.7), rifampicin 1.2 (0.9-1.5), vancomycin > 90%.
[b] ED_{50} of comparator (teicoplanin) was 5.4 (4.3-6.9).
[c] ED_{50} of comparator (teicoplanin) was 0.79 (0.65-0.96).
[d] Confidence limit could not be calculated because survival was either 0 or 100% in each treatment group.

Endocarditis experiments can be performed in experiment animals (rats) with isolates of staphylococci or enterococci. A polyethylene catheter is inserted through the aortic valve into the left ventricle of the animal via the right carotid artery. Two days later, the animals are infected i.v. Treatment begins the day after infection and continues for a total of 5 days. Surviving animals are killed on day 7 after infection. The hearts of all animals are homogenized and processed to determine bacterial load, that is expected to be substantially reduced in the treatment group receiving the formulations of the invention, in particular in comparison with the conventional i.v. formulations of the same active principle.

Pneumonia experiments can be performed in both immunocompetent and neutropenic rats with e.g. a clinically isolated penicillin-resistant *Strep. pneumoniae* strain. Anesthetized animals are infected by surgical intrabronchial instillation via intratracheal intubation, with a 40 µl inoculum containing approximately 10^6 to 10^7 log_{10} CFU (colony forming units) of *Strep.pneumoniae* and are allowed to recover. Therapy is initiated 12 h after infection and continued for a total of three days. Surviving animals are killed on day 5 after infection. The lungs of all animals are homogenized and processed to determine bacterial load, that is expected to be substantially reduced in the treatment group receiving the formulations of the invention, in particular in comparison with the conventional i.v. formulations of the same active principle.

The results reported above show that the formulations of the invention are in general well tolerated, in particular at the injection site, as demonstrated by the absence of necrotic inflammation and urine discoloration.

The results indicate that the delivered drug is effective in treating infections caused also by multiresistant microorganisms.

The formulations of the invention therefore can be effectively administered to a patient in need thereof to control or cure infections sustained by microorganisms that are known to be susceptible to ramoplanin or an antibiotic of the ramoplanin family.

Particularly preferred is the use of the formulations of the invention in antibiotic treatment of serious Gram positive infections such as bacteremia, endocarditis and lobar pneumonia. In particular the use of the formulations of the invention is specially suitable for systemic treatment of severe infections caused by Gram positive resistant or multiresistant microorganisms, such as coagulase-positive and negative staphylococci, penicillin resistant streptococci or glycopeptide resistant enterococci.

In the present disclosure, the term "patient" is intended to refer to warm blooded animals such as rodents, felines, equines, bovids, and primates, including humans. Preferred as "patients" according to the invention, in addition to humans, are pet and farm animals.

Troughout this description and claims the percentages are intended to be by weight (i.e. w/w) unless otherwise specified.

An example of dosage range of ramoplanin or a member of the ramoplanin family that can be administered through formulation of the invention, that is predicted to be effective for human therapy, is preferably between 0.5 and 1 g/die, while a preferred formulation contains about 5 mg/ml of ramoplanin.

Particularly preferred is the use of the formulations of the invention in severe enterococcal infections, particularly those attributable to vancomycin-resistant strains, for which no really effective treatment is currently available (see for instance M.B. Edmond et al., Clinical Infectious Diseases, 1996; 23: 1234-1239) as well as infections wherein penicillin-resistant streptococci are present.

In such treatments, the formulation of the invention is preferably employed as a slow infusion by a central vein.

The formulations of the invention are prepared according to the conventional techniques, on the basis of the present disclosure. The pH of the final preparation is lower than 7 and preferably between 4 and 6.5, with a pH between 5.5 and 6.5 being currently most preferred.

If necessary the pH of the final formulation is adjusted to the desired value by the known procedures.

Examples of specific formulations of the invention and formulation procedures are reported below.

Table IV. Formulations of Ramoplanin (10 mg/ml) in varying dilutions of Intralipid.

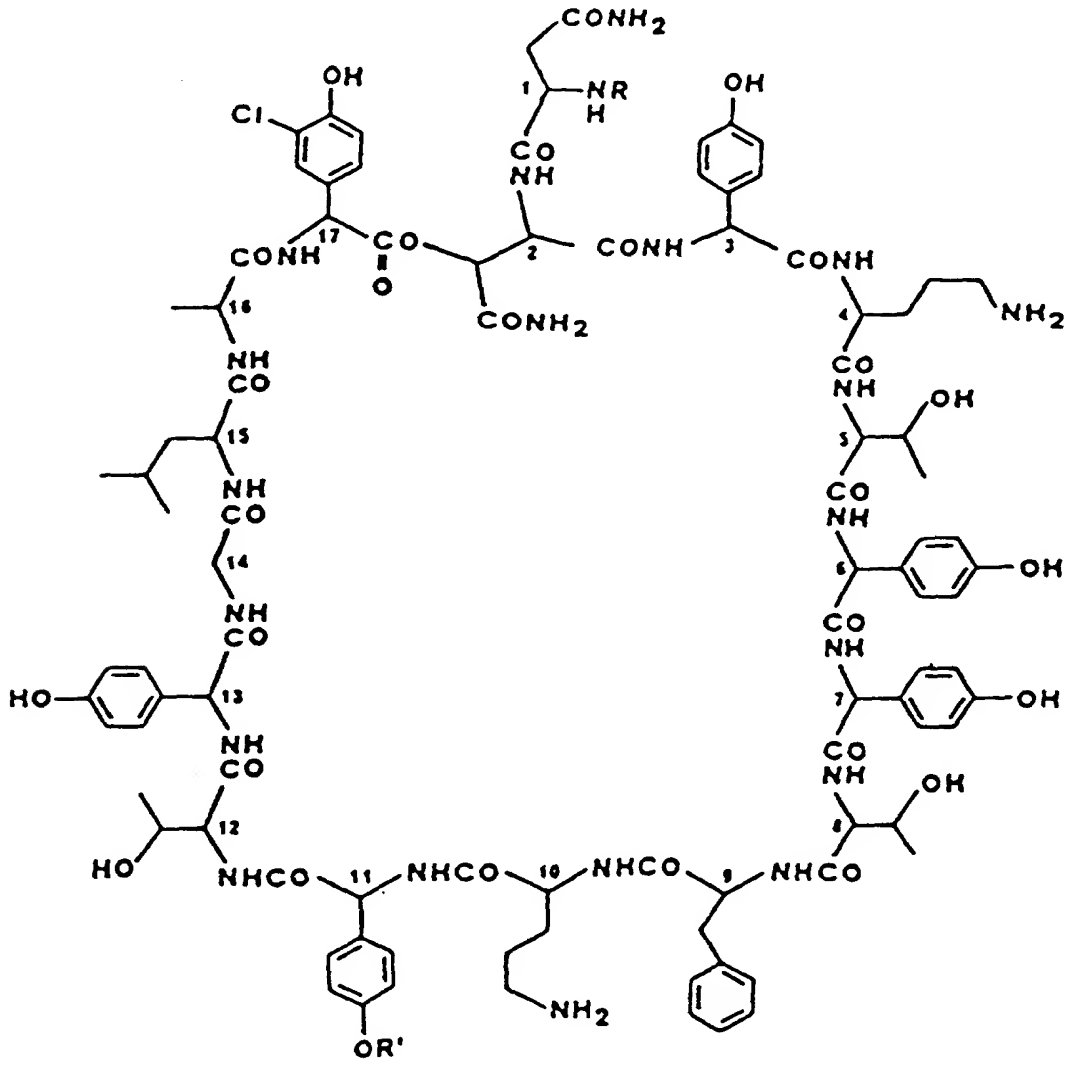
	10% Intralipid (ml)	5% Glucose (ml)	50 mg/ml Ramoplanin (ml)	Intralipid / Ramoplanin
A	8	--	2	8% / 10 mg/ml
B	4	4	2	4% / 10 mg/ml
C	2	6	2	2% / 10 mg/ml

Operatively, to a 10% dilution of Intralipid (Pharmacia), under moderate stirring, the glucose solution is slowly added followed by the ramoplanin solution.

The solution of ramoplanin in distilled water is prepared by dissolving 562 mg of ramoplanin (89% potency determined by a HPLC assay) in distilled water (5 ml) and then bringing to the final volume (10 ml).

CLAIMS

1. Pharmaceutical formulation for intravenous administration which comprises ramoplanin or a member of the ramoplanin family of formula I



FORMULA I

Wherein:

R represents $-CO-CH=CH-CH=CH-CH_2-CH_2-CH_3$,
$-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,
$-CO-CH=CH-CH=CH-CH_2-CH_2-CH(CH_3)_2$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$,
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH(CH_3)_2$ or
$-CO-CH_2-CH_2-CH_2-CH_2-CH_2-CH2-CH(CH_3)_2$

R' represents alpha-D-mannopyranosyl or 2-O-alpha-D-mannopyranosyl or

R' represents 2,3-O-di[alpha-D-mannopyranosyl]-D-mannopyranosyl and R represents $-CO-CH=CH-CH=CH-CH_2-CH(CH_3)_2$,

a pharmaceutically acceptable acid addition salt thereof, or a mixture thereof in any proportion.

in admixture with a fat emulsion product for intravenous administration at a concentration of at least 4%.

2. A formulation according to claim 1 wherein the emulsion product comprises vegetable oils and phosphatides.

3. A formulation according to claim 1 wherein the emulsion product comprises vegetal oils such as soybean and safflower oil, phospholipids such as egg yolk phospholipids, glycerin, fatty acids such as linolei, oleic, palmitic, linolenic or stearic acid and any mixture thereof.

4. A formulation according to claim 1 wherein the emulsion product comprises a composition selected from those reported in the following tables:

5

	Fat emulsion Product 1	Fat emulsion product 2	Fat emulsion product 3
Soibean oil	10%	20%	5%
Safflower oil	--	--	5%
Egg yolk phospholipids	1.2%	1.2%	1.2%
Glycerin	2.25%	2.25%	2.5%
Fatty acids:			
Linoleic acid	50%	50%	65.8%
Oleic acid	26%	26%	17.7%
Palmitic acid	10%	10%	8.8%
Linolenic acid	9%	9%	4.2%
Stearic acid	3.5%	3.5%	3.4%
Osmolarity (mOsm/L)	260	268	276
Approximate pH	8	8	8
Fat particle size (μm)	0.5	0.5	0.4
Caloric value (cal/ml)	1.1	2.0	1.1
Size (ml)	5, 100	50, 100	25, 50
	250 or	250 or	100,200
	500	500	Or 500

	Fat emulsion Product 4	Fat emulsion product 5	Fat emulsion product 6
Soibean oil	10%	10%	20%
Safflower oil	10%	--	--
Egg yolk phospholipids	1.2%	1.2%	1.2%
Glycerin	2.5%	2.5%	2.5%
Fatty acids:			
Linoleic acid	65.8%	54.5%	54.5%
Oleic acid	17.7%	22.4%	22.4%
Palmitic acid	8.8%	10.5%	10.5%
Linolenic acid	4.2%	8.3%	8.3%
Stearic acid	3.4%	4.2%	4.2%
Osmolarity (mOsm/L)	258	284	292
Approximate pH	8.3	8.3	8.3
Fat particle size (µm)	0.4	0.4	0.4
Caloric value (cal/ml)	2.0	1.1	2.0
Size (ml)	25, 50	100,200	200 or
	200 or	Or 500	550
	500		

and water for injection q.s. to 100%.

5. A formulation according to any one of claims 1 to 4 wherein the concentration of the fat emulsion product is between 4 and 25% (w/w) of the final formulation.

6. A formulation according to claim 5 wherein the concentration of the fat emulsion product is between 8 and 20% (w/w) of the final formulation.

7. A formulation according to claim 5 wherein the concentration of the fat emulsion product is between 8 and 18% (w/w) of the final formulation.

8. A formulation according to any one of claims 1 to 7 wherein ramoplanin is present at a concentration between 5 and 10 mg/ml.

9. A formulation according to any of claims 1 to 8 wherein the pH of the final formulation is lower than 7.

10. A formulation according to any of claims 1 to 7 wherein the pH of the final formulation is between 4 and 6.5.

11. A formulation according to any one of claims 1 to 10 for treatment of infections caused by agents that are susceptible to ramoplanin or an antibiotic of the ramoplanin family.

12. A formulation according to any one of claims 1 to 10 for the treatment of serious Gram positive infections such as bacteremia, endocarditis or lobar pneumonia.

13. A formulation according to any one of claims 1 to 10 for the treatment of severe infection caused by Gram positive drug-resistant or multiresistant microorganisms such as coagulase positive and negative staphylococci, penicillin-resistant streptococci or glycopeptide resistant enterococci.

14. A formulation according to any one of claims 1 to 13 wherein ramoplanin factor A_2 is present in an amount of at least 75%.

ABSTRACT

The present invention relates to a new injectable formulation of ramoplanin or a compound of the ramoplanin family. More particularly, the injectable formulations of the invention are particularly suitable for intravenous (i.v.) administration. They contain the active principle(s) in a fat emulsion product for i.v. administration.

The formulations of the invention are well tolerated and are effective in particular in severe Gram positive infections.